IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA CORP., PHARMACIA & UPJOHN INC., PHARMACIA & UPJOHN COMPANY, G.D. SEARLE & CO., G.D. SEARLE LLC, SEARLE LLC (DELAWARE) and SEARLE LLC (NEVADA) Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC. Defendant.	)	**CONFIDENTIAL - OUTSIDE ATTORNEYS' EYES ONLY** Civil Action No: 04-754 (JCL) **DRAFT June 22, 2006**

REBUTTAL EXPERT REPORT OF DR. HENRY G. GRABOWSKI

I submit this report pursuant to Fed. R. Civ. P. 26 to set forth the opinions I have formed and may offer at trial of this action.

I. MATERIALS CONSIDERED

1. In forming my opinions and preparing this report, I have reviewed and relied upon the materials cited and listed in Exhibit A, attached to this report, the materials cited and listed in my first expert report, and my many years of study of economics and the pharmaceutical industry. This work is reflected in my publication list.[1]

II. SUBJECT MATTER ABOUT WHICH I EXPECT TO TESTIFY

2. In addition to the subjects addressed in my first report, I presently plan to give opinions and testimony concerning the following topics:

[1] Grabowski Rep., Ex. A.

a. Pharmaceutical innovation is the cornerstone of the research-based pharmaceutical industry;

b. Celebrex® was successful because it satisfied an unmet medical need;

c. Celebrex® enjoyed unprecedented success attributable to its novel properties;

d. Celebrex® marketing is not the primary reason for its extraordinary success;

e. Celebrex® achieved and maintains its blockbuster status despite substantial negative publicity; and

f. Teva's expert reports are replete with unsubstantiated and incorrect statements.

3. I may address other matters in response to reports or other evidence offered by Teva. I reserve the right to supplement my report with additional IMS data for 2006. Accordingly, I attach a revised Exhibit 9 which includes 2006 data for Mobic®.

4. I reserve the right to supplement or amend my opinions in response to opinions expressed by defendant's experts, or in light of any additional evidence, testimony, discovery or other information relating to the aforementioned issues that may be provided to me after the date of this report. I further reserve my right to rely on any documents used by Teva's experts. In addition, I expect that I may be asked to consider and testify about issues that may be raised by defendant's experts in their reports or at trial. In connection with my testimony, I may rely upon certain graphic or demonstrative exhibits that have not yet been prepared.

III. INNOVATION

5. Innovation is the cornerstone of the brand-name, research-based pharmaceutical industry. Innovators spend billions of dollars on research every year in the hope of coming up with a blockbuster drug. Only a small number of compounds that are studied by

research-based firms will have the necessary efficacy and safety to gain FDA approval.[2] I have conducted research showing that, in 2000 dollars, the cost of the research and development for a new drug that gained marketing approval was more than $800 million.[3] Pharmaceutical companies depend on sales from this one potential blockbuster to recoup their investments on their numerous failed compounds. A pharmaceutical company's success is dependant upon its ability to create innovative and valuable new products.

IV. CELEBREX® WAS A SUCCESSFUL DRUG BECAUSE IT SATISFIED AN UNMET MEDICAL NEED

6. As explained in my first report, the first report of Dr. Galbraith, and the report of plaintiff's witness Dr. Helfgott, the need for a safer NSAID was well known for decades.[4] The dissatisfaction among patients with the effectiveness of the existing NSAIDs resulted in a great deal of patients switching NSAIDs. This precipitated the search for a more effective treatment.[5]

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2 *See, e.g.* U.S. Food and Drug Administration, *"Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products,"* March 2004, p. 8 ("a new medicinal compound entering Phase I testing, often representing the culmination of upwards of a decade of preclinical screening and evaluation, is estimated to have only an 8 percent chance of reaching the market.")(PFC01598212-48).

3 DiMasi, Hansen, & Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 2003, 22: 151-185 (PFC01607006-41).

4 Grabowski Rep. ¶16; Galbraith Rep. ¶19; Helfgott Rep. ¶22.

5 Paulus and Furst, Arthritis and Allied Conditions - A Textbook on Rheumatology. Chapter 28. Aspirin and other Nonsteroidal Anti-inflammatory Drugs, p. 479 ("If the patient has an inadequate therapeutic response, the first drug should be replaced with a second NSAID, and the process should be repeated.") (PFC01579032-67).

7. There was a belief in 1999 among scientists and physicians that the demand for a safer NSAID might be met by a COX-2 Selective NSAID.[6] The failure of previous products to satisfy the need for a safer NSAID and the belief by scientists and physicians that COX-2 Selective NSAIDs would provide a safety advantage over other Non-Selective NSAIDs, resulted in a demand for a COX-2 Selective NSAID.[7] Celebrex® and Vioxx® were the first compounds that selectively inhibited COX-2 at therapeutic levels in humans, while not inhibiting COX-1.[8]

8. The FDA acknowledged that Celebrex® represented an advance over previous NSAIDs. I understand that the NDA for Celebrex® was filed on June 29, 1998[9] and was selected for Priority review by the Food and Drug Administration ("FDA").[10]. New Drug Applications ("NDAs") are designated for either Standard or Priority review.[11] A Priority designation is intended for those products that address unmet medical needs. The FDA guidelines describing a Priority review are set forth in the Manual of Policies and Procedures, Center For Drug Evaluation and Research ("MAPP"). The MAPP defines a Priority review as:

> The drug product, if approved, would be a significant improvement compared to marketed products . . . in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for

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6 *See, e.g.*, Brooke, "Cox-2 Inhibitors: Big Market; Big Battle; Big Issues," *Morgan Stanley Dean Witter* (1998), PFC01579924-PFC01579942, pp. 1-2 (PFC01579924-25).

7 S*ee, e.g.*, Brooke, "Cox-2 Inhibitors: Big Market; Big Battle; Big Issues," *Morgan Stanley Dean Witter* (1998), PFC01579924-PFC01579942, p. 6 (PFC01579929).

8 Seibert Rep. ¶¶61-65.

9 PFC00756191-PFC00756193 (December 31, 1988 Letter from DeLap to Begley).

10 CDER NME Approvals in Calendar Year 1999 (http://www.fda.gov/cder/rdmt/NDAPriority99.htm) (PFC01602677-9).

11 MAPP 6020.3, p. 1 (PFC01603507-10).

> example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new subpopulation.[12]

Further, the policy set forth in the MAPP for a Priority review is:

> A "priority" designation is intended to direct overall attention and resources to the evaluation of applications for products that have the potential for providing significant preventative or diagnostic therapeutic advance as compared to "standard" applications.[13]

Therefore, in granting Celebrex® a Priority review, the FDA believed (as did scientists and physicians) that Celebrex®, if approved, could represent a major advance over existing NSAIDs.

9. I further understand that the Non-Selective NSAIDS launched in the 1990's prior to Celebrex® (Arthrotec®, Daypro®, and Relafen®) or subsequent to Celebrex® (Mobic®) were not granted Priority review.[14]

V. WHEN CELEBREX® WAS LAUNCHED, IT ENJOYED UNPRECEDENTED SUCCESS

10. Celebrex® was the first drug to achieve $1 billion in sales in its first year on the market and was the most successful product launch ever.[15] Through 2005, in just seven

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[12] MAPP 6020.3, pp. 1-2 (PFC01603507-10).

[13] MAPP 6020.3, p. 2 (PFC01603507-10).

[14] www.fda.gov/cder/da/da1297.htm (Drug Approvals for December 1997) (Arthrotec®); www.fda.gov/cder/da/ddpa.htm (1991 Drug and Device Product Approvals) (Relafen®) www.fda.gov/cder/da/ddpa.htm (1992 Drug and Device Product Approvals) (Daypro®) www.fda.gov/cder/da/da0400.htm. (Mobic®)

[15] *See, e.g.,* Goodman, "Chief Scientist Has Built Reputation on Success," *St. Louis Post-Dispatch,* December 26, 1999 ("Celebrex® . . . is the most successful new-product launch the pharmaceutical industry has ever seen.") (PFC01606504-6); Stein, "Pharmacia & UpJohn, Monsanto to Merge...", *The Los Angeles Times*, December 20, 1999 ("Celebrex had the most successful introduction in history.") (PFC01606661-2); Burton, "Arthritis Drug Won't be Named in Ads for Monsanto Product," *The Wall Street Journal*, May 4,

years on the market, Celebrex® has generated more than $15.7 billion in U.S. sales. As discussed below, Celebrex®'s commercial success is largely attributable to its properties.

A. Celebrex®'s Novel Properties as a COX-2 Inhibitor Explain Its Commercial Success

11. The properties of a drug – namely safety and efficacy – are the most important factor driving the sales of any pharmaceutical.[16] The market seeks and rewards improvements in product quality.[17] New products that offer greater effectiveness or safety can overtake competitors in the market because of physicians' desire to prescribe the most effective treatment for their patients. As stated above, there was an expectation among scientists and physicians that COX-2 Selective NSAIDs would provide an improved safety profile over existing NSAIDs. I see nothing in the reports of Teva's experts that addresses the likelihood that Celebrex® is commercially successful because of this expectation. The mere fact that, several years after the introduction of Celebrex®, a debate began over the existence and degree of the safety advantage Celebrex® has over other NSAIDs does not support a conclusion that the commercial success Celebrex® achieved is unrelated to the properties of the drug. Dr. Leffler has not provided any evidence to the contrary.

1999, p. B13; Burton, "Monsanto's Arthritis Drug Sells Briskly," *The Wall Street Journal*, Feb. 10, 1999, p.1.

[16] *See, e.g.,* Booth and Zemmel, "Quest for the Best," *Nature*, 2003, 2: 838-841, 839, Figure 1 (examining "thirty two blockbusters launched by 15 of the top pharmaceutical companies during 1991-2000") (PFC01602622-6).

[17] *See, e.g., Id.*.

B. Celebrex® Has Greater Persistence than Vioxx® and Non-Selective NSAIDs

12. I understand that, in the search for an NSAID that provides the appropriate efficacy and safety profile, patients commonly switch between NSAIDs.[18] Dr. Helfgott identifies the practice of "[p]atient switching between available NSAIDs," as "'the NSAID shuffle.'"[19] Dr. Helfgott speculates, based on his personal experience, that "patients using Celebrex® switched therapies due to symptoms of gastrointestinal side effects or lack of therapeutic efficacy" at the same rate that they switched from other NSAIDs[20] demonstrating, in his eyes, that Celebrex® was no better than other NSAIDs. Dr. Helfgott's speculation, however, does not agree with the available evidence.

13. Published studies demonstrate that Celebrex® has a longer duration of use and "time to switch" than Vioxx® and Non-Selective NSAIDs.

(a) Wolfe, et al.[21] conducted a study of 3639 patients who had a diagnosis of rheumatoid arthritis (RA), osteoarthritis (OA) of the hip or knee, or fibromyalgia, and report that survival times of celecoxib (15 months) and rofecoxib (13 months) differed significantly from those of naproxen and ibuprofen (both 10 months), and celecoxib had a longer survival time than rofecoxib.[22] Wolfe, et al. state that duration of use can be an

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18 Paulus and Furst, Arthritis and Allied Conditions - A Textbook on Rheumatology. Chapter 28. Aspirin and other Nonsteroidal Anti-inflammatory Drugs, p. 479 ("If the patient has an inadequate therapeutic response, the first drug should be replaced with a second NSAID, and the process should be repeated.") (PFC01579032-67).

19 Helfgott Rep. ¶33.

20 Helfgott Rep. ¶34.

21 Wolfe et al., "Longer Use of COX-2 Specific Inhibitors Compared to Nonspecific Nonsteroidal Antiinflammatory Drugs: A Longitudinal Study of 3639 Patients in Community Practice," *J. Rheumatol.*, 2004, 31:355-58 (PFC01605615-8).

22 *Id.*

indicator of treatment effectiveness and/or drug acceptability, and their results may suggest that celecoxib is more effective and acceptable than Non-Selective NSAIDs.

(b) Zhao, et al.[23] conducted a study of the "time to switch" of 20,049 RA and OA patients using COX-2 Selective NSAIDs (celecoxib and rofecoxib) and Non-Selective NSAIDs. The authors state that "time to switch" may be used to evaluate the overall effectiveness of a drug:

> Switching in the context of chronic diseases such as rheumatoid arthritis and osteoarthritis, is an indicator of overall effectiveness of drug therapy in usual clinical practice.[24]

The study found that the time to 25% switching was longer for celecoxib (205 days) and rofecoxib (159 days) compared to the Non-Selective NSAIDs (49-78 days).[25] The study also reported that "COX-2 specific inhibitors are being targeted to patients at higher risk of GI adverse events.[26]

14. Although these studies have their limitations,[27] they demonstrate that arthritis patients stayed on Celebrex® longer than Vioxx® and Non-Selective NSAIDs. The differences are statistically significant. In particular, these studies conclude that Celebrex® may be a more effective treatment option for arthritis patients, in the usual clinical practice setting, relative to Non-Selective NSAIDs.

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23 Zhao, et al., "Drug switching patterns among patients with rheumatoid arthritis and osteoarthritis using COX-2 specific inhibitors and non-specific NSAIDs," *Pharmacoepidemiology and Drug Safety*, 2003, 13:277-87 (PFC01185330-40).

24 Zhao, et al., p. 284.

25 Zhao, et al., p. 287.

26 Zhao, et al., p. 285.

27 Luggen, "Trials are Short, Disease Long: Measuring Drug Utility Beyond Clinical Trials," *J. Rheumatol.*, 2004, 31:2, pp. 205-06; Zhao, et al., pp.285-86 (.

C. Insurers and Payors Influence Drug Product Demand

15. In the United States, insurance coverage for outpatient drugs is paid for primarily by employer health care plans. Pharmacy Benefit Managers ("PBMs") have emerged in the last decade as the main overseers of the prescription drug plans of employees and managed care organizations.[28] PBMs have developed various strategies for controlling prescription drug consumption and the attendant costs, including formularies, mandatory generic substitution programs, three-tier co-payment schemes, prior authorization, drug utilization reviews, and rebates from drug manufacturers/suppliers.

16. Drug formularies are lists of approved drugs that will be reimbursed by the payor to the patient/pharmacy when prescribed for a given medical problem. A prevalent type of formulary currently employed in the United States is a three-tier system of co-payments. Under this structure, drugs in the same therapeutic class are classified into three tiers. Generic drugs are in Tier 1 and have the lowest co-payment (and therefore the largest percentage of cost that the HMO or insurer will pay for any drug). Preferred branded drugs are in Tier 2. These are generally drugs for which there is no generic equivalent and are covered by the HMO or insurance company. Non-preferred drugs are in Tier 3 and have the highest co-payment, if they are covered by the HMO or insurance company at all.[29] There are variations in this three-tier system among different HMOs and third-party payors, and the terminology sometimes differs. In essence, however, all formularies use a system that provides the highest reimbursement for the

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[28] According to a 2000 PhRMA report, 82% of pharmaceutical prescriptions were reimbursed at least in part by third party payors. (PhRMA 2000 Pharmaceutical Industry Profile, p.66).

[29] *See* Grabowski & Mullins, "Pharmacy Benefit Management, Cost-Effectiveness Analysis, and Drug Formulary Decisions," *Social Science and Medicine*, 45 (1997), 535-44; Winslow, McGinley, & Adams, "Healing the System," *Wall Street Journal*, September 11, 2002.

lowest cost drug product among a number of drugs that are close substitutes therapeutically. The higher cost drug will either not be covered at all, or covered only with a higher co-payment.

17. The process of assigning branded drugs to the middle or highest tier of a formulary is usually based on both therapeutic and economic considerations. Most PBMs and managed care organizations ("MCOs") follow a two-step process. First, the Pharmacy and Therapeutics Committee for a PBM or MCO will determine whether a new product should be reimbursed on medical grounds and, if so, whether there are close therapeutic substitutes for this product. If a product does have close substitutes, then the decision on which product should be placed in the preferred tier will generally be made on economic grounds (e.g., based on drug cost including rebates and discounts).[30] Branded drugs with generic equivalents will almost always be placed in Tier 3.[31]

18. Given the growing importance of managed care and its strategies for controlling prescription costs, one would expect a new drug offering minimal advantages over existing, lower-priced competitors to fare poorly in the marketplace. If Celebrex® were nothing more than a high-priced me-too NSAID, facing competition that was already genericized or about to be genericized, managed care organizations would have strong incentives to utilize formularies and prior authorization to restrict demand for Celebrex®. Instead, as discussed above, Celebrex® enjoyed the most successful product launch of any drug in history.

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30 *See* Grabowski and Mullins.

31 Some plans have mandatory generic usage or require payment by the consumer for the full cost difference between the branded drug and its lowest cost generic equivalent, if the consumer elects a branded drug in lieu of the generic form. *See* Grabowski and Mullins.

VI. THE ROLE OF MARKETING

A. The Marketing of New Pharmaceuticals Provides Important Information Benefits to Physicians and Patients

19. The function and benefit of marketing is to make physicians and the public aware of new medicines and treatments. Marketing is important for the diffusion of information on new pharmaceutical products into the medical world. The economics literature has consistently found that marketing by pharmaceutical firms provides physicians with valuable information about the uses and characteristics of pharmaceutical products, which has the effect of enhancing public welfare. One of the earliest contributions to this literature was by Dr. Leffler, who concluded his 1981 paper by stating:

> The empirical results presented here show that product promotion has a significant positive effect on the entry success of therapeutically important new drugs. Given the large potential social benefits from the more rapid adoption of superior drug therapies, restrictions on pharmaceutical promotion appear to risk large losses in consumer welfare for the promise of unproven and perhaps nonexistent gains.[32]

In a more recent study, Gonul, et. al.'s analysis of pharmaceutical promotion "helps disperse the concerns that personal selling is ethically objectionable because it might inordinately affect physicians. We find no evidence of such influence, and our findings suggest that detailing and free samples are mostly informative and increase price sensitivity."[33]

20. The pharmaceutical market is complex. For pharmaceutical companies to be successful, they generally need to address the market through several different approaches.

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[32] Leffler, "Persuasion or Information? The Economics of Prescription Drug Advertising," *Journal of Law and Economics*, Vol. 24, No. 1 (1981), pp. 61-74, 74 (PFC01607124-55) (Leffler Exhibit 19).

[33] Gonul, et. al., "Promotion of Prescription Drugs and Its Impact on Physicians' Choice Behavior," *Journal of Marketing*, Vol. 65 (July 2001), pp. 79-90, 89 (PFC01607081-92) (Leffler Exhibit 6).

The following activities are among those used by pharmaceutical companies when promoting a new drug: (a) detailing (presentations to doctors by a salesperson); (b) providing medical information to physicians and other providers; (c) providing samples and patient starter kits; (d) direct-to-consumer (DTC) advertising; and (e) advertising in medical journals.

21. These and other activities are standard in the industry. Research-based pharmaceutical companies would be hard pressed to market their new products without engaging in these activities because they would not be able to convey the necessary information to the physicians and prompt patients to ask their doctors questions about the risks and benefits of different medications. I understand that physicians would not use a product unless they were both aware of it and convinced of its usefulness through education (often gleaned from marketing) and then experience (their own and that of their colleagues).[34] Thus, without marketing, medical advances would not make their way into the marketplace efficiently.

22. As stated above, the actual properties of the product being marketed are the most important aspect of pharmaceutical marketing. Although it is unlikely that a pharmaceutical product can be successful without marketing activities, these marketing activities alone will not turn an ordinary drug–one that does not offer substantial benefits relative to competing products – into a "blockbuster." The principal consumers of pharmaceuticals are physicians, who are necessarily well-educated and highly trained. If a product does not deliver as promised, physicians will not adopt it or continue to use it.[35] It is the efficacy and safety of the product that, in the long run, determines its use and success.[36]

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[34] Iannini Rep. ¶28.

[35] Iannini Rep. ¶28.

[36] Booth and Zemmel, "Quest for the Best," *Nature*, 2003, 2: 838-841, 838 (PFC01602622-6).

B. Celebrex®'s Marketing Activity Was Not Extraordinary by Industry Standards

23. I have analyzed the marketing activities (details and samples) and promotional expenditures of Celebrex® compared to all COX-2 Selective (Vioxx®, Bextra®) and Non-Selective (Mobic®) NSAIDs launched from 1999 through the present.[37] I have also examined Celebrex®'s and Vioxx®'s DTC advertising. This analysis does not support Dr. Leffler's contention that Celebrex®'s "extraordinary" marketing effort was responsible for its unprecedented success.

24. Because marketing efforts vary by company and drug due to a variety of factors (including drug novelty, expected market potential, etc.), it is more meaningful to compare marketing ratios than absolute numbers. A more appropriate comparison (and the comparison that is accepted in the economics and marketing literatures)[38] is of the ratio of the marketing efforts and expenditures to both U.S. sales and U.S. prescriptions. Furthermore, since pharmaceutical marketing is more intensive in the initial years after launch, it is also appropriate to compare competitive products at similar points in their product life cycle. My analysis of marketing intensities in the NSAID market shows that Celebrex® actually had lower marketing to sales (and prescriptions) ratios than the other COX-2 Selective and Non-Selective NSAIDs.

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[37] Additionally, I was able to obtain information for Years 2-6 on the details and U.S. sales of the two most successful (based on U.S. sales) Non-Selective NSAIDs launched from 1992-1999, Relafen® and Daypro®.

[38] Ernst R. Berndt and colleagues have written a series of papers that adopt this measure. *See, e.g.*, Berndt, "Pharmaceuticals in U.S. Health Care: Determinants of Quantity and Price," *Journal of Economic Perspectives*, Vol. 22, No. 4 (Fall 2002) (PFC01607627-48), 52-54. Dr. Leffler also uses this measure in his 1981 paper. *See* Leffler, "Persuasion or Information? The Economics of Prescription Drug Advertising," *Journal of Law and Economics*, Vol. 24, No. 1 (April 1981), pp. 61-74, 74 (PFC01607124-55) (Leffler Exhibit 19).

Nevertheless, even the existence of substantial marketing efforts does not, by itself, demonstrate that the product would be successful if it lacked advantageous properties.

(i) Marketing to Physicians - "Detailing"

25. Given the sophisticated and complex nature of pharmaceutical products, the advertising and promotional efforts to market pharmaceutical products are largely directed at the ultimate decision maker, the physician. I understand that, without significant marketing, physicians would not easily become aware of new products; physicians rely on pharmaceutical marketing along with the literature for information on new medicines.[39]

26. Detailing is the practice of meeting with individual physicians and other medical professionals in their offices in a one-to-one setting to communicate about the specific features of the products, such as safety and efficacy. I understand that the primary purpose (and effect) of detailing is to provide information to the physician regarding the drug.[40] I further understand that much of the information provided during detailing relates to the safety and efficacy of the drug as demonstrated by clinical studies and other relevant scientific information.[41] I also understand that the impact of detailing efforts differs significantly and the greater the ability of a pharmaceutical company to communicate the therapeutic benefits of a drug and differentiate it from rival products based on the properties of the product, the greater the likelihood that it will be prescribed.[42]

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[39] Iannini Rep. ¶¶24-28; 70-76.

[40] *See, e.g.,* Gonul "Promotion of Prescription Drugs and Its Impact on Physicians' Choice Behavior," Journal of Marketing, Vol. 65 (July 2001), pp. 79-90, 90 (PFC01607081-92) (Leffler Exhibit 6); *see also* Iannini Rep. ¶¶24-28; 70-76.

[41] *See, e.g.,* Iannini Rep. ¶¶24-28; 70-76.

[42] *See, e.g.,* Booth and Zemmel, "Quest for the Best," *Nature*, 2003, 2: 838-841 (PFC01602622-6); *see also* Iannini Rep. ¶¶24-28; 70-76.

27. As demonstrated in Exhibit 10 below, Celebrex®'s ratio of details/$1000 of U.S. sales was lower than the ratio of each of its competitor drugs in each of the first five years after launch, during which time Celebrex® generated $11.3 billion in U.S. sales (a figure which, by itself, demonstrates a substantial commercial success). For example, in Year 1, Celebrex®'s ratio of details/$1000 in U.S. sales was 1.5 times lower than Vioxx®, 2.5 times lower than Bextra®, and more than 4 times lower than Mobic®. Thus, in Year 1, Mobic® preformed 4 times as many details as Celebrex® per thousand dollars in U.S. sales. Although Mobic®'s ratio of details/$1000 of U.S sales fell below Celebrex®'s in one year out of six, this did not occur until Year 6, and does not account for the unparalleled success Celebrex® displayed over the first five years. Similar results are observed when examining the ratio of details to U.S. prescriptions.[43]

28. Celebrex® also performed better than the two most successful (based on U.S. sales) Non-Selective NSAIDs launched from 1992-1999. Celebrex®'s ratio of details/$1000 in U.S. sales was two to four times lower than the ratios for Relafen® and Daypro®. I conclude that the strong market response to Celebrex®'s novel characteristics allowed for a more efficient detailing to sales ratio for Celebrex®, compared to each of the competitors measured. The trends illustrated in Exhibits 10 and 11 contradict Dr. Leffler's contention that extraordinary marketing occurred for Celebrex® and this is the reason for its commercial success.

(ii) Provision of Samples

29. Another way that pharmaceutical companies market their products is by providing samples to physicians for distribution to patients. Exhibit 12 demonstrates that Celebrex®'s ratio of samples/$100 in U.S. sales was significantly lower than each of the

[43] *See* Exhibit 11.

competing drugs for the first five years after launch, again demonstrating that Celebrex® sampling was more productive than the sampling of each of the competitors analyzed.

30. In Year 1, Celebrex®'s ratio of samples/$100 in U.S. sales was 1.5 times lower than Vioxx®, 2.5 times lower than Bextra®, and more than 4 times lower than Mobic®. In Years 2-5, Celebrex®'s ratio of samples/$100 in U.S. sales was consistently lower than each of the competing products. In Year 6, Celebrex®'s ratio of samples/$100 in U.S. sales was lower than Vioxx® and roughly equal to Mobic®. Similar results are seen when comparing the ratio of samples to U.S. prescriptions.[44] As with detailing, I conclude that the low sampling to sales ratio of Celebrex®, compared to competing NSAIDS, is an indicator of the strong market response to novel characteristics.

(iii) Promotional Expenditures

31. It is also relevant to examine the ratio of total promotional expenditures to sales revenues. In Exhibit 14, total promotional expenditures include product expenditures on details, journal advertising, professional medical information, and DTC advertising. As demonstrated by Exhibit 14 below, in Years 1-5, Celebrex®'s promotional and marketing expenditures as a percentage of U.S. sales were consistently the lowest of each of the competing products brought to market before (or after) the launch of Celebrex®.

(iv) DTC Advertising

The Effect of DTC Advertising Is Small and Increases Therapeutically Appropriate Use of the Advertised Drug

32. Dr. Leffler acknowledges that DTC advertising can inform consumers of an available treatment and cause them to discuss the treatment of their pain with their

[44] *See* Exhibit 12.

physicians.[45] Although Dr. Leffler states that the effect of DTC advertising is to increase demand,[46] he ignores the conclusions of the empirical literature (including literature that he cites in his report) that the effects of DTC advertising are relatively small and that DTC advertising has the effect of increasing therapeutically appropriate use of the advertised drugs. In a recent paper, Iizuka also finds that firms do more DTC advertising when drugs are new, high quality, and when the untreated population is large.[47]

33. Economists who have conducted empirical investigations of the effects of DTC advertising on pharmaceutical sales have concluded that, while DTC advertising does increase sales, the effects are relatively small. Rosenthal, et. al., conclude that DTC advertising accounted for about 12% of the growth in total prescription drug expenditures between 1999 and 2000, and that "DTC advertising is important, but not the primary driver of recent growth."[48] Wosinska finds that DTC advertising increases sales of anti-cholesterol drugs only if those drugs are included on insurance company formularies. She concludes that: "The high ratio of fulfilled drug requests is driven less by patient's influence than physician's existing preference for these

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45 Leffler Rep., ¶12.

46 Leffler Rep., ¶13

47 Toshiaki Iizuka, "What Explains the Use of Direct-to-Consumer Advertising of Prescription Drugs," *The Journal of Industrial Economics*, Vol 52, No. 3 (September 2004), 349-379.

48 Rosenthal, et al., "Demand Effects of Recent Changes in Prescription Drug Promotion," June 2003, pp. 1-33, 19 (PFC01604139-74)(Leffler Exhibit 28).

drugs."[49] Iizuka and Jin find that DTC advertising has little effect on the choice of brand of non-sedating antihistamine.[50]

34. The literature also suggests that increased DTC advertising leads to increases in therapeutically appropriate prescribing. One paper cited by Leffler that studies the effects of DTC advertising for antidepressants concludes that, while patient requests for specific products did result in increased prescription of that product, they also increased the likelihood that patients would receive minimally acceptable treatment rather than inadequate treatment.[51] Another study, which examines the effects of DTC advertising on the use of COX-2 Selective NSAIDs, concludes:

> This evidence suggests these effects may be welfare enhancing, in that advertising tends to encourage more rapid adoption among patients who are good clinical candidates for the therapy, and leads to less rapid adoption among some patients who are poor clinical candidates.[52]

35. Dr. Leffler does cite one paper that purports to show that patients who saw or heard a DTC ad and asked their doctors about Celebrex® or Vioxx® were significantly more

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[49] Wosinska, "Just What the Patient Ordered? Direct-to-Consumer Advertising and the Demand for Pharmaceutical Products," Harvard Business School Marketing Research Paper No. 02-04, October 2002 (PFC01605650).

[50] Iizuka and Jin, "Direct to Consumer Advertising and Prescription Choice," 4/4/05 (PFC01607097-116).

[51] Kravitz, et al., "Influence of Patients' Request for Direct-to-Consumer Advertised Antidepressants: A Randomized Controlled Trial, *JAMA*, Vol. 293, No. 16 (April 27, 2005) , 1995-2002. (PFC01603268-76)(Leffler Exhibit 17).

[52] Bradford, et al., "The Effect of Direct to Consumer Television Advertising on the Timing of Treatment," August 8, 2005 (PFC01602627-62).

likely to receive an inappropriate prescription for a COX-2 Selective NSAID.[53] This paper does not investigate the possibility that patients who mention Celebrex® or Vioxx® to their doctors are likely to be patients who have not experienced good results with competing NSAIDS. Thus what appears to the authors to be "inappropriate" prescribing may in fact be an appropriate use of COX-2 Selective NSAIDs for patients who have not found relief from other NSAIDS. In my opinion, this paper's failure to consider this alternative explanation renders its conclusions invalid.

DTC Advertising Did Not Cause Celebrex®'s Commercial Success

36. Pfizer did not launch Celebrex® with a DTC campaign. Rather, I understand from Pfizer internal documents that DTC advertising for Celebrex® was only briefly conducted in May-June 1999 (after Celebrex® had already become the best selling prescription NSAID and after the launch of Vioxx®).[54] This DTC effort consisted of a 15-second reminder ad.[55] Pfizer implemented an "ad hiatus" in July-August 1999,[56] and did not resume DTC advertising until September 1999.[57] Thus, Celebrex® had achieved more than $800 million in U.S. sales before Pfizer engaged in any significant DTC advertising.[58] I also understand that

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53 Spence, et al., "Direct-to-Consumer Advertising of COX-2 Inhibitors: Effect on Appropriateness of Prescribing, *Medical Care Research* Review, Vol. 62, No. 5 (October 1, 2005), 544-559. (PFC01604283-98)(Leffler Exhibit 31).

54 PFC00338348; 1999 DTC data, Verispan, PSA, HPSA, DTCA/CMR.

55 PFC00338348; 1999 DTC data, Verispan, PSA, HPSA, DTCA/CMR.

56 PFC00338350; *see also* 1999 DTC data, Verispan (showing no Celebrex® DTC spending in July-August 1999).

57 PFC00338348;1999 DTC data, Verispan, PSA, HPSA, DTCA/CMR.

58 PFC01593451-PFC01593453 (1999 IMS data, "National Sales Perspectives").

television advertising for Celebrex® did not begin until January 2000.[59] Moreover, Pfizer's internal documents show that, when marketing surveys were conducted following the January 2000 start of television advertising, consumers reported an increased "awareness" of the Celebrex brand, but only reported using Celebrex® at levels that "had not grown" since late August 1999 — during the Celebrex® "ad hiatus."[60] I further understand that Pfizer ceased DTC advertising altogether in December 2004.[61] Thus, Celebrex®'s $1.6 billion in sales in 2005 cannot be attributable to DTC advertising.[62]

37. Furthermore, there is no evidence that "patients who ask questions, or who make suggestions, on the basis of advertisements,"[63] received prescriptions for Celebrex® solely because of this request, or that physician-patient conversations did not result in a discussion of the advantages of Celebrex® relative to other NSAIDs. Dr. Leffler, citing an internal Pfizer document, states, "Pfizer research found that 1 in 4 Celebrex® users had requested Celebrex® from their doctors, and the likelihood that a requesting patient would receive a Celebrex® prescription was 97% [sic.]."[64] Even if one were to assume that all of the prescriptions issued to those patients were solely a result of patient requests (and not because of the relative advantages of Celebrex®), that still leaves 75% of Celebrex® sales that are not attributable to DTC advertising.

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59 PFC00338350.

60 PFC00338350.

61 December 20, 2004 FDA Statement on Celebrex® DTC Promotion (http://www.fda.gov/bbs/topics/news/2004/new01147.html)(PFC01598275).

62 Grabowski Rep., Ex. 1.

63 Leffler Rep. ¶12.

64 Leffler Rep. ¶20. I note that the correct figure is 94%. *See* PFC01236170.

38. Moreover, as demonstrated in Table 1, Celebrex® had significantly less DTC advertising than Vioxx® in each of its first two years on the market.[65]

Table 1[66]

	Year 1	Year 2	Total DTC Spending ($) For Years 1-2
Celebrex®	$27,648,000	$78,261,000	$105,909,000
Vioxx®	$84,153,000	$129,799,000	$213,952,000

Following Dr. Leffler's reasoning that DTC advertising plays a central role in inducing pharmaceutical sales,[67] one would have expected Vioxx® to have attained significantly more prescriptions than Celebrex® during its first two years, all else equal. As demonstrated in Exhibit 11 however, Celebrex® received significantly more prescriptions during its first two years on the market than did Vioxx®, indicating that DTC advertising does not have the dominant effect on sales claimed by Dr. Leffler.

39. Finally, I disagree with Dr. Leffler that there is any proven correlation between the decline in Celebrex®'s U.S. sales in 2005 and "the cessation of continuing Celebrex® DTC promotion."[68] Dr. Leffler ignores the substantial negative publicity experienced by all COX-2 Selective NSAIDs in 2004 and the Black Box warning placed on Celebrex® and all other prescription NSAIDS (as discussed in more detail below) as a possible cause for the decline in sales. In order to make such a conclusion, one would have to conduct either a

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65 In 2000, Vioxx® spent more on direct to consumer advertising than any other drug on the market in the U.S – $50 million more than the next highest drug and more than $80 million more than Celebrex®. (2000 Pharmaceutical Market Performance and Promotion Summary), (PFC01594749).

66 1999-2001 DTC data, Verispan, PSA, HPSA, DTCA/CMR.

67 Leffler Rep. ¶13.

68 Leffler Rep. ¶30.

comprehensive survey of patients and physicians to determine the reasons they decided to switch off of or not initiate therapy with Celebrex® or conduct an econometric analysis that would control for confounding influences. Dr. Leffler has made no such effort.

VII. CELEBREX® ACHIEVED AND MAINTAINS ITS BLOCKBUSTER STATUS DESPITE SUBSTANTIAL NEGATIVE PUBLICITY

40. Since long before withdrawal of Vioxx® in September 2004, Celebrex® has been receiving negative publicity – both questioning its gastrointestinal safety advantages and alleging cardiovascular risks – in the popular press, which is available to physicians as well as patients.[69] I understand that, in light of the withdrawal of Vioxx® due to cardiovascular safety concerns in September 2004, the FDA convened a panel to evaluate the safety of all NSAIDs. I further understand that these hearings resulted in a Black Box Warning being placed on Celebrex®, and all other prescription COX-2 Selective and Non-Selective NSAIDs.

41. The fact that Celebrex® was able to withstand the negative publicity, including that associated with the well publicized FDA hearings in February 2005 and the withdrawal of both Vioxx® and Bextra® (the only two other COX-2 Selective NSAIDs), as well as the negative connotations associated with a Black Box Warning, and still achieve $1.6 billion in U.S. sales is a testament to its commercial success.

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[69] *See, e.g.,* Maugh, "Study Finds Heart Risks in Popular Arthritis Medicines Vioxx, Celebrex," *Los Angeles Times*, August 22, 2001, at A15 (PFC01606654-6); Kritz, "You and A: Arthritis Drugs; Pain and Confusion," *Washington Post*, Sept. 4, 2001, at F01 (PFC01606507-9); Associated Press, "Study Questions Effectiveness of Celebrex, 2 Other Arthritis Drugs," *Los Angeles Times*, Dec. 26, 2002, at 17 (PFC01606490-1); O'Connor, "Vioxx, Celebrex, Now Aleve. What's a Patient to Think?" *NY Times*, Dec. 28, 2004, at F5 (PFC01606657-60).

VIII. TEVA'S EXPERT REPORTS ARE REPLETE WITH UNSUBSTANTIATED AND INCORRECT STATEMENTS

A. There is No Evidence That Celebrex®'s Commercial Success "Was Heavily Influenced by Advertising and Promotion"

42. Dr. Helfgott makes numerous unsubstantiated statements in his expert report with respect to the marketing efforts surrounding Celebrex® and the effect those efforts had on physicians and patients.

43. First, Dr. Helfgott makes two statements by which he purports to speak on behalf of all physicians. Dr. Helfgott states that "Pfizer was notorious among physicians for having an aggressive, broad base of sales representatives, particularly among primary care physicians"[70] and "[P]hysicians were reluctant to tell patients that an over the counter NSAID was as effective as Celebrex."[71] Dr. Helfgott provides no basis for his statements. Conclusions summarizing the opinions of physicians and the reasons for prescribing decisions must be based on well-conducted surveys. Dr. Helfgott has neither conducted such a survey nor relied on a survey conducted by another.

44. Second, there is no evidence that Celebrex®'s DTC advertising "created an unrealistic expectation on the part of chronic pain sufferers as to how well their pain medication should make them feel."[72] The documents Dr. Leffler cites do not support his statement. The article by Groopman was published on June 15, 1998, more than 6 months before Celebrex® was launched and more than a year before Pfizer commenced DTC advertising. Moreover, there is

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[70] Helfgott Rep. ¶ 43.

[71] Helfgott Rep. ¶47.

[72] Helfgott Rep. ¶46.

no evidence that the Groopman article had any actual impact on prescribing decisions or patient or doctor expectations.

45. The January 10, 2005 untitled letter from the FDA addresses some DTC pieces, but does not address the actual impact they had on consumers. A statement regarding the expectation that DTC advertising created in patients would require an extensive survey of patients to determine what expectation they had, whether it was based on DTC advertising, and if the expectation was unrealistic. Dr. Helfgott has neither conducted nor cited to any such survey. Furthermore, any problems with respect to DTC advertising addressed in the January 10, 2005 letter would have had no effect on the huge commercial success that Celebrex® enjoyed starting in January 1999.

46. Third, Dr. Helfgott states, in examining only the pre-launch market, that, with Celebrex®, Pfizer "faced little competition in marketing their drug to physicians and patients."[73] Similarly, Dr. Leffler states that "the lack of significant marketing for NSAID prescription pharmaceuticals" attributed to Celebrex®'s commercial success. Drs. Helfgott and Leffler do not provide any supporting evidence establishing that Celebrex®'s commercial success is attributable to the lack of marketing by other prescription NSAIDs, and ignore the substantial marketing efforts of the competing NSAIDs on the market prior to the launch of Celebrex® as well as the marketing campaign launched by Vioxx® only months after Celebrex® came to market.

47. Several new products were launched in the 1990's - Arthrotec®, Daypro® and Relafen®.[74] These NSAIDs were accompanied by significant marketing efforts. For

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[73] Helfgott Rep. ¶45.

[74] PFC01594332 (1999 Pharmaceutical Market Performance & Promotion Summary).

example, as shown in the Table 2 below, Relafen® (launched in February, 1992) and Daypro® (launched in January, 1993)[75] were among the top thirty most detailed drugs on the market from 1994-1998, and often ranked among the top 20. This fact does not comport with Drs. Leffer and Helfgott's characterization of the prescription NSAID market as lacking significant marketing.

Table 2

	Rank Among Prescription Drugs Based on Number of Details[76]				
Drug	**1994**	**1995**	**1996**	**1997**	**1998**
Relafen®	26	14	18	27	29
Daypro®	9	7	15	20	30

48. Similarly, Drs. Leffler and Helfgott ignore the marketing campaign that was launched by Vioxx® in May 1999. Vioxx® spent nearly the same amount on promotion and marketing as Celebrex® in its first year on the market.[77] Thus, Celebrex®: (a) entered an NSAID market comprising products that had been significantly detailed for years prior to its launch; and (b) quickly faced competition from new products – Vioxx® and later Mobic®.

49. In addition, simply because some NSAIDs did not engage in significant marketing in the years immediately preceding and following the launch of Celebrex® does not mean that those products did not (or were not able to) compete with Celebrex®. There may not have been a need to market many of the older NSAIDs because drugs such as aspirin, ibuprofen and naproxen had already become so well known through prior advertising and dissemination of

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75 *See, e.g.,* PFC01594332 (1999 Pharmaceutical Market Performance & Promotion Summary).

76 PFC01594039 (1994 Market Performance & Promotion Summary); PFC01594113 (1995 Market Performance & Promotion Summary); PFC01594451 (1997 U.S. Market Performance & Promotion Summary); PFC01594298 (1998 Pharmaceutical Market & Performance Summary).

77 *See* Exhibit 14.

information about those drugs over time. As explained below, significant marketing for Celebrex® (a first-in-class drug) was needed to educate consumers regarding the efficacy and safety of it its new, unprecedented mechanism of action, which differed from other NSAIDs that had the benefit of years of prescribing experience to support the safety of their mechanism(s) of action.

B. There Is No Basis for Attributing the Commercial Success of Celebrex® to "Improper" Advertising

50. Dr. Leffler states that the commercial success of Celebrex® was due to Pfizer's misleading advertising.[78] Dr. Leffler provides no analysis of the impact of the "improper" advertising on sales. An analysis of the impact that the "improper" advertising had on sales of would require, at a minimum, determining the number of health care professionals who received the pieces, determining the number of prescriptions they wrote, and contacting each physician to determine how many of the prescriptions they wrote resulted from the "improper" advertising. Drs. Leffler and Schultz have made no attempt to conduct this type of analysis and instead make the unsupported assertion that Celebrex®'s commercial success is attributable only to those advertising pieces that were objected to by the FDA.

51. Furthermore, I understand that the first letter Pfizer received from the FDA after the launch of Celebrex® was dated October 6, 1999. The pieces addressed in this letter could not have been responsible for the $800 million dollars in U.S. sales that Celebrex® achieved in its first eight months.[79]

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[78] Leffler Rep. ¶27.

[79] *See* PFC01593451-PFC01593567 (1999-2000 IMS data, "National Sales Perspectives")

C. The CLASS Manuscript Was Not Responsible for Celebrex®'s Extraordinary Commercial Success

52. Celebrex® was a blockbuster long before the publication of the CLASS Manuscript in September 2000, having already achieved more than $2.7 billion in its first twenty months on the market (January 1999-August 2000).[80]

53. Dr. Wolfe ignores Celebrex®'s established commercial success and instead states that Celebrex®'s "remarkable 18.8% increase" in sales between 2000 and 2001 was the result of the publication of the CLASS trial manuscript. There is no basis for this statement.[81] Dr. Wolfe does not cite a single study demonstrating that the increased sales of Celebrex® in 2001 were attributable to publication of the CLASS trial manuscript in September 2000. Proving this point would require some attempt to investigate the relative impacts of the CLASS manuscript, Celebrex®'s novel properties, the positive experience of consumers and physicians with Celebrex®, etc. Dr. Wolfe, however, makes no attempt to carefully consider the possible contributors to Celebrex®'s sales and determine the relative impacts of each. Instead, he simply assumes that all of the increase in Celebrex® sales that occurred after the CLASS manuscript was published must have been attributable to the effects of the manuscript. Moreover, Dr. Wolfe ignores the fact that the purported 18.8% increase from 2000-2001 was over 34% less than the increase from the previous year (1999-2000), before the CLASS manuscript had been published.

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80 PFC01593451-PFC01593453 (1999 IMS Data, "National Sales Perspectives"); PFC01593532-PFC01593567 (2000 IMS Data, "National Sales Perspectives")

81 Similarly, Dr. Leffler cites a quote from an FDA director that "[t]he *JAMA* article is believed to have had significant impact on Celebrex sales." (Leffler Rep. ¶34). Neither Dr. Leffler nor the article he cites provide any quantitative support for this statement.

D. Celebrex®'s Commercial Success Is Not Attributable to Being a "New Prescription NSAID"

54. Dr. Helfgott states that new prescription NSAIDs "often acquire a significant share of new prescriptions because patients who had not been treated successful [sic] on pre-existing NSAID therapies would be switch [sic] to try any new NSAID in hopes that it did alleviate the pain."[82] Similarly, Dr. Leffler states that "[t]his willingness to try a 'new' NSAID provided an opportunity to Celebrex® to achieve significant sales independent of any meaningful therapeutic advantages or differences with existing treatments."[83] Neither Dr. Leffler nor Dr. Helfgott provide any support for their statements.

55. Even if it occurred, this switching to a "new" NSAID does not account for Celebrex®'s commercial success in its first year or its continued success over its lifetime. As shown in Figure 1, below, the number of new prescriptions (NRx) for any of the previously launched Non-Selective NSAIDs – Arthrotec®, Voltaren®, Relafen®, Feldene®, Lodine®, Daypro®, Ansaid®, Lodine XL®, Naprosyn®, EC-Naprosyn®, and Voltaren XR® – was at best 400,000 NRx per month and often averaged much lower.[84]

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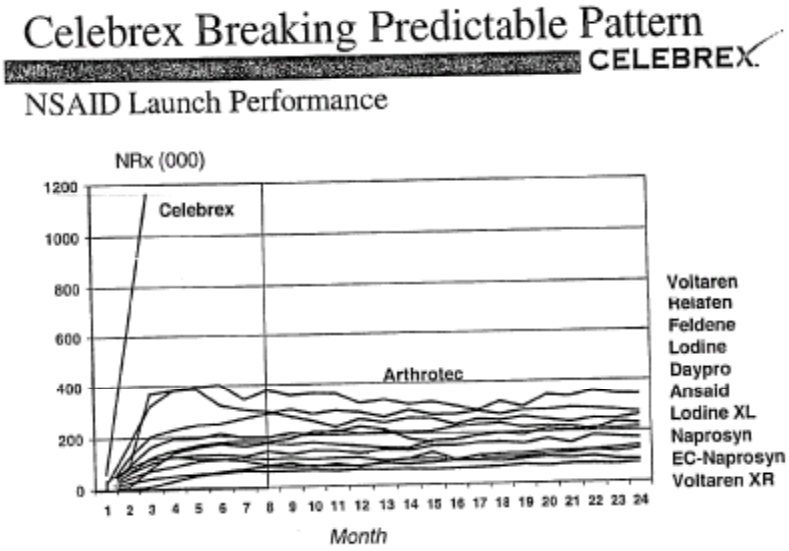
82 Helfgott Rep. ¶ 36.

83 Leffler Rep. ¶10.

84 *See* PFC0119743.

Figure 1[85]



In contrast, Celebrex® achieved more than 1.1 million new prescriptions per month in only its third month on the market and averaged roughly 1.0 million new prescriptions through the end of its second year.[86] Accordingly, typical switching does not account for Celebrex®'s unprecedented (in the NSAID market) success from launch.

56. Moreover, if the willingness to try a "new" NSAID can create significant sales "independent of any meaningful therapeutic advantages or difference with existing treatments" one would have expected Mobic® (launched after Celebrex® in May, 2000) to have achieved significant new prescriptions similar to Celebrex® and Vioxx®. Instead, Mobic® never reached 100,000 new prescriptions per month in its first year on the market, remaining well below the average for other branded, prescription NSAIDs.[87]

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85 PFC01191743.

86 1999-2005 IMS, NRx data

87 1999-2005 IMS, NRx data

E. There is No Evidence That Celebrex®'s Commercial Success is Due to a Preference for Treating With Prescription Medicines

57. Dr. Leffler states "physicians seeing patients seeking pain relief are expected to prefer to treat these patients with prescription medicines, *available only by visiting the physician*, as this retains the value of the services of the physician."[88] Dr. Leffler does not provide support for his assertion or make any attempt to conduct the type of analysis required to support such a statement. Moreover, Celebrex® has always competed with other prescription NSAIDs available only by prescription (*e.g.*, Arthrotec®, Mobic®), including some NSAIDs that are available as cheaper generics (*e.g.*, Daypro® (oxaprozin), Relafen® (nabumetone), Voltaren®/VoltarenXL® (diclofenac sodium)).

58. In addition, Dr. Leffler's statement is directly at odds with the actual prescribing habits of physicians in the NSAID market. If physicians preferred to treat their patients with medication that was not available over the counter, then, upon the introduction of Celebrex® and Vioxx® in 1999, one would have expected the number of prescriptions for Daypro®, Relafen®, Arthrotec® (those drugs available only by prescription)[89] to have been greater than the number of prescriptions for ibuprofen and naproxen (which were available over-the-counter, albeit at lower doses). However, the exact opposite is true. In 1998, prescriptions for ibuprofen (22.6 million) were 2.5 times greater than those for Relafen® (8.7 million), 4 times greater than those for Daypro® (5.7 million), and nearly 8 times greater than those for Arthrotec® (2.9 million).[90] Similar results are seen with naproxen (16.2 million).[91] Indeed, from 1999-2004

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88 Leffler Rep. ¶9 (emphasis added).

89 Leffler Rep. ¶16.

90 Grabowski Rep., Ex. 3.

91 Grabowski Rep., Ex. 3.

ibuprofen was the second highest prescribed drug (third in 2001), second only to Celebrex®.[92] In 2005, ibuprofen was the most prescribed drug.[93]

F. There is No Evidence that the "First Mover Advantage" Is Responsible for Celebrex®'s Commercial Success

59. In the pharmaceutical industry, being best-in-class rather than first-in-class is what ultimately determines the success of a drug. Booth and Zemmel conducted a study of "thirty two blockbusters launched by fifteen of the top pharmaceutical companies during 1991-2000," and found that "75% were directed against clinically validated pharmacological targets."[94] Booth and Zemmel concluded:

> Much of the industry's past value creation has come not from first-in-class drugs against completely new targets, but from follow-on drugs that improve the efficacy or reduce the side effects of existing compounds. Most of the industry's blockbuster drugs have been developed as best-in-class clinical innovations, and only rarely were they 'discovered' as first-in-class agents.[95]

60. Dr. Leffler concludes, without any support, that Celebrex®'s ability "to sustain sales in the face of competitive entry is the result of a first-mover advantage that has nothing to do with any therapeutic advantage or invention." As stated above, it is the properties of the drug, not its marketing or the order of its entry, that determines its ultimate success. For example, Lipitor® overtook other statins because of its superior efficacy on lowering cholesterol

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92 Grabowski Rep., Ex. 3.

93 Grabowski Rep., Ex. 3.

94 Booth and Zemmel, "Quest for the Best," *Nature*, 2003, 2: 838-841, 838 (PFC01602622-6).

95 Booth and Zemmel, "Quest for the Best," *Nature*, 2003, 2: 838-841, 838 (PFC01602622-6)

compared to the older statins.[96] Similarly, Zantac®, an anti-ulcer medication, overtook the first H2 antagonist despite its premium price, because it had fewer side-effects.[97] Thus, the significance of the "first-mover advantage" is unclear and there is no evidence that it was the cause of Celebrex®'s commercial success.

61. Although drugs that are first movers do, all else equal, have an advantage over subsequent competitors, that advantage is not absolute. As discussed above, if a follow-on drug is more effective or safer than the first mover, it is not uncommon for the "best-in-class" to overtake the "first in class." Furthermore, recent research by DiMasi and Paquette has shown that the amount of time first movers are sheltered from competition has declined precipitously since the 1970's, reflecting a decline in the barriers to entry for follow-on drugs.[98] The authors identify both supply side factors, such as technological advances in basic biomedical research, and demand side factors, such as the increased price sensitivity caused by the spread of managed care, as explanations for the decline in the first-mover advantage over time. Celebrex® was introduced only four months prior to Vioxx®, leaving it little time to exploit any first mover advantages.

62. Moreover, Dr. Leffler ignores the disadvantages associated with being a first-mover relative to established products. Because a firm with a first-in-class drug must

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96 Booth and Zemmel, "Quest for the Best," *Nature*, 2003, 2: 838-841, 839; *See also* PFC01594466 (1997 U.S. Market Performance & Promotion Summary); PFC01594340 (1998 Pharmaceutical Market Performance & Promotion Summary); PFC01594645 (1999 Pharmaceutical Market Performance & Promotion Summary); PFC01597193 (2005 U.S. Pharmaceutical Market Performance & Promotion Summary).

97 Moore, "Pharmaceuticals - Interesting Times in a Cyclical Industry" (http://www.buildingipvalue.com/06/intro/019_022.htm).

98 Joseph A. DiMasi and Cherie Paquette, "The Economics of Follow-on Drug Research and Development," *Pharmacoeconomics*, Vol. 22 Suppl. 2 (2004), 1-14.

develop the market for a new category of products, it educates the physicians and patients as to the properties of the new class. Consequently, there is often a "spillover" effect in marketing, and much of the advertising will be attributed to the class of drugs. Thus, competing products will benefit from the efforts of the pioneer to promote the drug. Since Vioxx® was on the market four months after Celebrex®, it is likely that Vioxx® benefited from the early advertising conducted by Pfizer.

G. The Success of Vioxx® Does Not Preclude a Finding that Celebrex® Is a Commercial Success

63. Dr. Leffler suggests that Celebrex® cannot be a commercial success because "within a few months after its entry, physicians were writing as many prescriptions for Vioxx® as for Celebrex®."[99] I disagree. The U.S. NSAID market accounted for more than $3.6 billion in U.S. sales in 1999 and $6.5 billion in U.S. sales at its peak in 2004.[100] There is no basis for concluding that only one drug can be a commercial success within a given market. In any event, Celebrex® has had much more commercial success than Vioxx® based on: (a) its cumulative present value[101] and (b) the fact that Vioxx® was voluntarily withdrawn from the market based on cardiovascular safety concerns, while Celebrex® remains the only COX-2 Selective NSAID on the market in the United States.

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[99] Leffler Rep. ¶28.

[100] Grabowski Rep., Ex. 1.

[101] Grabowski Rep., Ex. 1.

H. The Launch of Celebrex® (and Vioxx®) Resulted in a Significant Decrease in Prescriptions of Non-Selective NSAIDs

64. Dr. Leffler states that "Celebrex has modest or no impact on typical NSAID volume." Dr. Leffler's statement is at odds with the data demonstrating that in 1998, prior to the launch of Celebrex®, Non-Selective NSAID prescription volume was 79.5 million and within two years (by 2000) had declined to 63.3 million.[103] Non-Selective NSAID prescription volume further declined to 59 million by 2003.[104]

65. Furthermore, Dr. Leffler provides no basis for his conclusion that "current users of other NSAIDs did not perceive significant advantages to Celebrex."[105]

Dated: June 23, 2006

Dr. Henry G. Grabowski

103 Grabowski Rep., Ex. 6.

104 Grabowski Rep., Ex. 6.

105 Leffler Rep. ¶31.

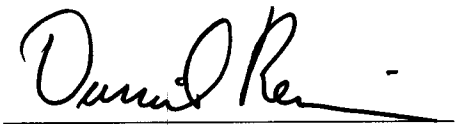
CERTIFICATE OF SERVICE

I hereby certify that I caused a true and correct copy of the foregoing Rebuttal Expert Report of Dr. Henry Grabowski to be served by electronic mail on the 23rd day of June 2006 on the counsel for the defendant as follows:

Thomas L. Creel
Keith A. Zullow
GOODWIN PROCTER LLP
599 Lexington Avenue
New York, NY 10022
Fax: 212-355-3333

I hereby certify that I caused a true and correct copy of the foregoing Rebuttal Expert Report of Dr. Henry Grabowski to be served by first class mail on the 26th day of June 2006 on the counsel for the defendant as follows:

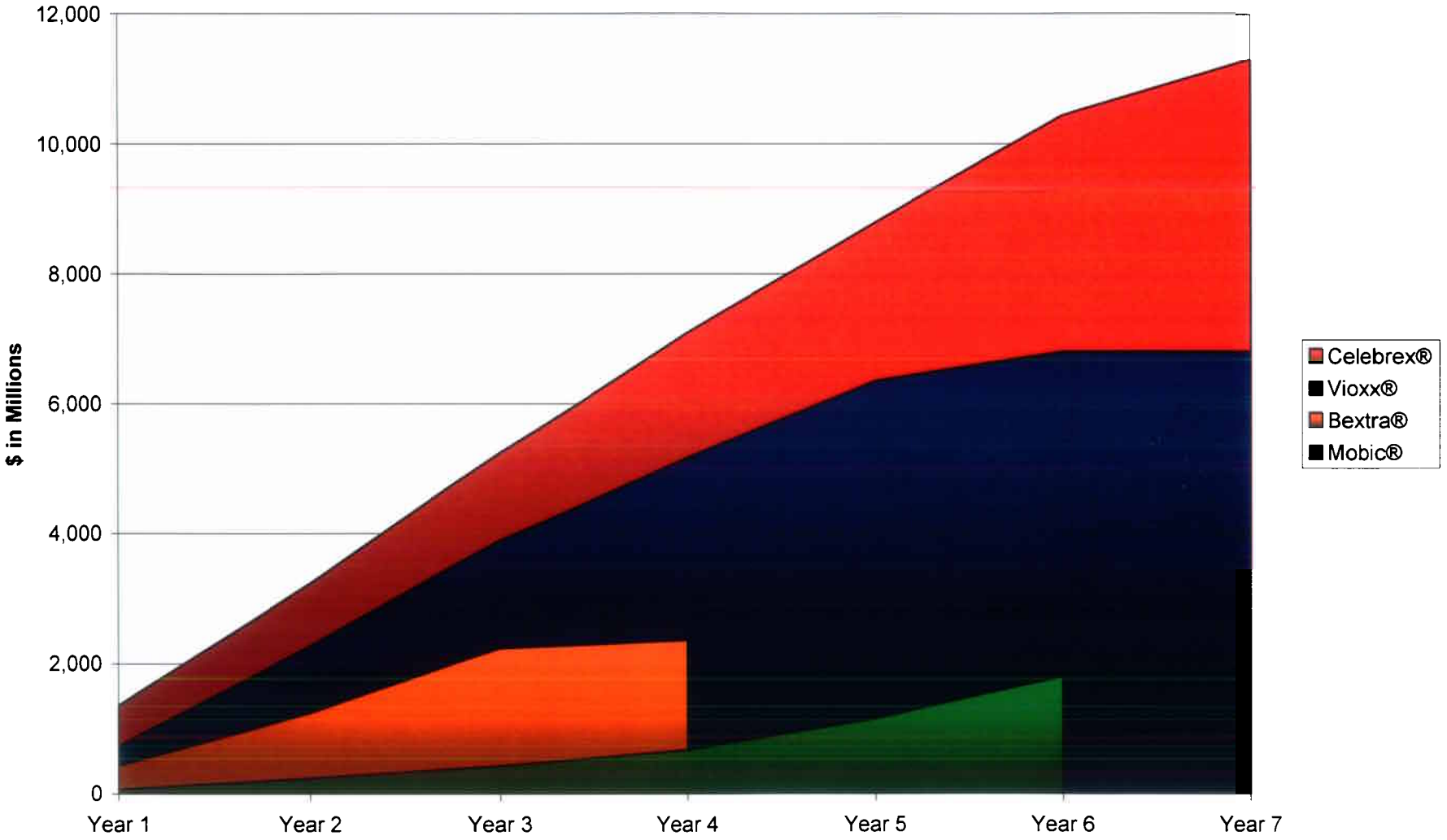
Thomas L. Creel
Keith A. Zullow
GOODWIN PROCTER LLP
599 Lexington Avenue
New York, NY 10022
Fax: 212-355-3333



Daniel Reisner

Exhibit 9

Revised Exhibit 9: Cumulative Present Value of U.S. Sales Discounted Back to the Year of Launch By Year Through April, 2006 of Four NSAIDs Launched From 1999-2005



Revised Exhibit 9: Cumulative Present Value of U.S. Sales Discounted Back to the Year of Launch By Year Through April 2006 of Four NSAIDs Launched From 1999-2005

Drugs	Cumulative ByYear in Year 1 Dollars						
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Celebrex®	1,352	3,230	5,239	7,091	8,785	10,435	11,295
Vioxx®	736	2,270	3,894	5,162	6,350	6,800	6,800
Bextra®	432	1,247	2,236	2,360			
Mobic®	70	240	432	678	1,158	1,802	

Discount Rate = 10% applied to discount all dollars to present value as of year 1 (launch)

Vioxx® was launched in May 1999.
Bextra® was launched in January 2002.
Mobic® was launched in May 2000.

*1999-2006 IMS data, "National Sales Perspectives."

Drugs	0	1	2	3	4	5	6	7
Celebrex®		1,418	2,167	2,549	2,586	2,600	2,787	1,598
Vioxx®		772	1,770	2,061	1,770	1,824	760	
Bextra®		453	940	1,255	174			
Mobic		73	197	243	344	736	1,083	

*1999-2006 IMS data, "National Sales Perspectives"

Present Value

Celebrex®	1352.01	1878.321	2008.575	1852.483	1693.192	1649.974	860.0512
Vioxx®	736.0731	1534.208	1624.038	1267.94	1187.839	449.9392	
Bextra®	431.9186	814.7771	988.9219	124.645			
Mobic	69.60277	170.7565	191.4805	246.4246	479.3036	641.1633	

Exhibit 10

Exhibit 10: Ratio of Details/$1,000 in U.S. Sales by Year from Launch

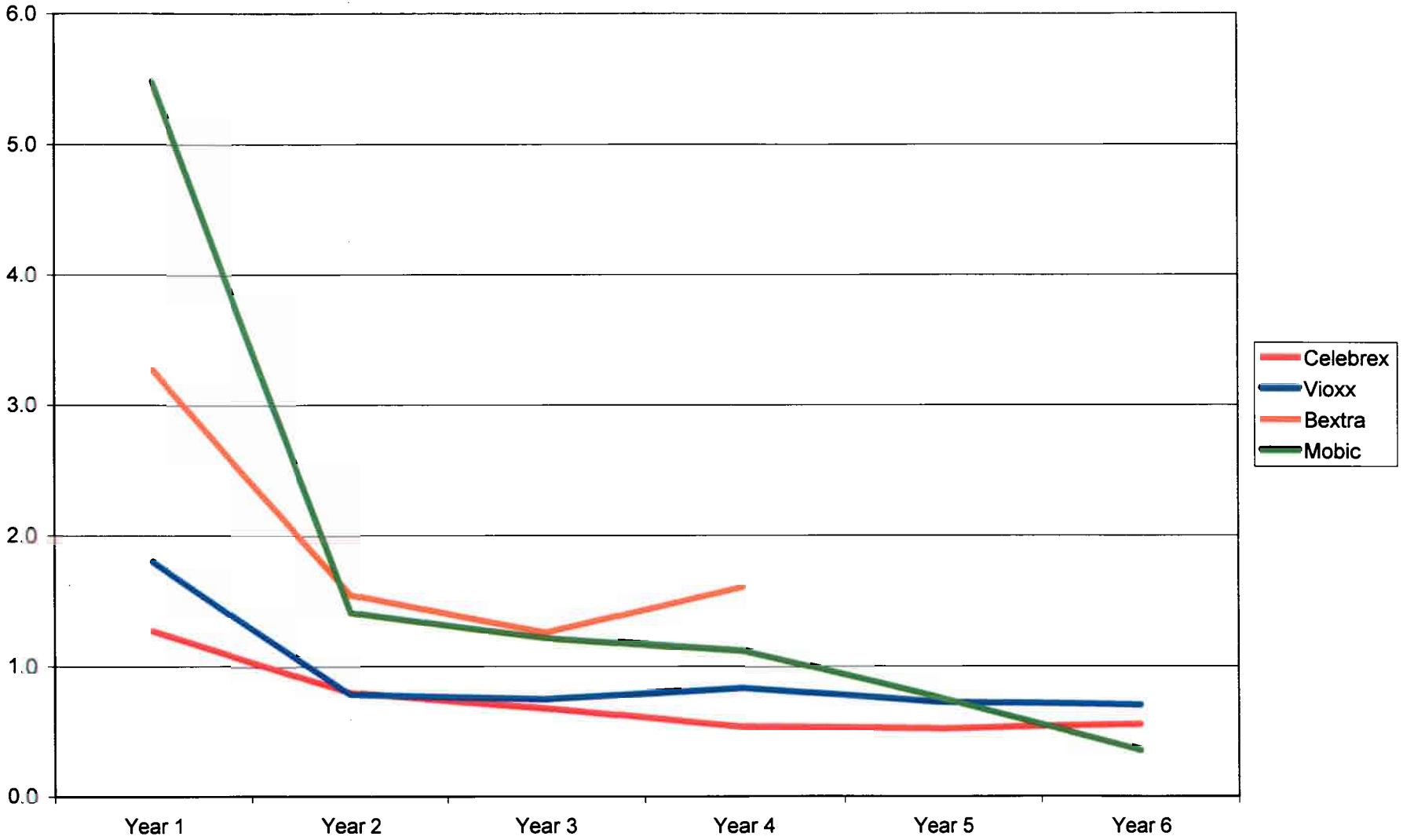


Exhibit 10

Number of Details By Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex*	1,809,000	1,738,000	1,747,000	1,402,000	1,373,000	1,569,000
Vioxx*	1,392,000	1,392,000	1,553,000	1,484,000	1,329,000	538,000
Bextra*	1,484,000	1,459,000	1,586,000	280,000		
Mobic*	400,000	279,000	297,000	386,000	558,000	392,000
Relafen**		590,000	452,000	424,000	448,000	395,000
Daypro***		639,000	572,000	517,000	479,000	439,000

* Source: 1999-2006 Verispan data, PSA, HPSA
** Source: PFC01594020(1993); PFC01594039(1994); PFC01594139(1995); PFC01594269(1996); PFC01594492(1997)
*** Source: PFC01594039(1994); PFC01594139(1995); PFC01594267(1996); PFC01594492(1997); PFC01594332(1998)

U.S. Sales By Year from Launch (in $ millions)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex*	1,418	2,167	2,549	2,586	2,600	2,787
Vioxx*	772	1,770	2,061	1,770	1,824	760
Bextra*	453	940	1,255	174		
Mobic*	73	197	243	344	736	1,083
Relafen**		247	313	354	389	420
Daypro***		179	247	289	307	319

* Source: 1999-2006 IMS data, "National Sales Perspectives"
** Source: PFC01594020(1993); PFC01594040(1994); PFC01594139(1995); PFC01594269(1996); PFC01594492(1997)
*** Source: PFC01594040(1994); PFC01594139(1995); PFC01594267(1996); PFC01594492(1997); PFC01594332(1998)

Ratio of Details/$1000 U.S. Sales by Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	1.3	0.8	0.7	0.5	0.5	0.6
Vioxx	1.8	0.8	0.8	0.8	0.7	0.7
Bextra	3.3	1.6	1.3	1.6		
Mobic	5.5	1.4	1.2	1.1	0.8	0.4
Relafen		2.4	1.4	1.2	1.2	0.9
Daypro		3.6	2.3	1.8	1.6	1.4

Exhibit 11

Exhibit 11: Ratio of Details/U.S. Prescriptions by Year From Launch

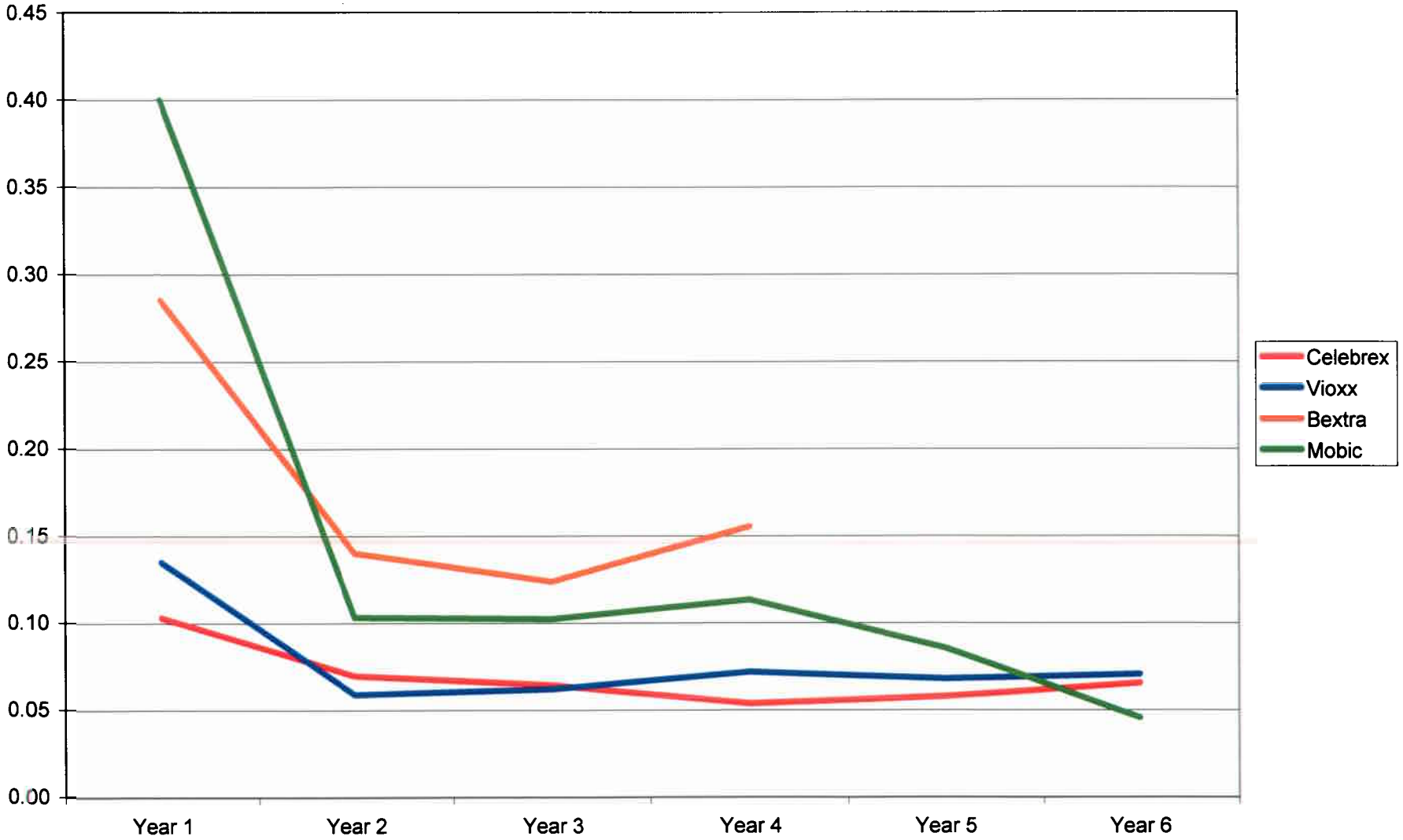


Exhibit 11

Number of Details By Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	1,809,000	1,738,000	1,747,000	1,402,000	1,373,000	1,569,000
Vioxx	1,392,000	1,392,000	1,553,000	1,484,000	1,329,000	538,000
Bextra	1,484,000	1,459,000	1,586,000	280,000		
Mobic	400,000	279,000	297,000	386,000	558,000	392,000

* Source: 1999-2006 Verispan, PSA, HPSA

Total U.S. Prescription By Year from Launch ('000)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex®	17,500	24,900	27,100	26,000	23,700	23,900
Vioxx®	10,300	23,600	25,000	20,600	19,500	7,600
Bextra®	5,200	10,400	12,800	1,800		
Mobic	1,000	2,700	2,900	3,400	6,500	8,600

* Source: 1999-2006 IMS data, "National Prescription Audit"

Ratio of Details/U.S. Prescriptions by Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	0.10	0.07	0.06	0.05	0.06	0.07
Vioxx	0.14	0.06	0.06	0.07	0.07	0.07
Bextra	0.29	0.14	0.12	0.16		
Mobic	0.40	0.10	0.10	0.11	0.09	0.05

Exhibit 12

Exhibit 12: Ratio of Samples/$100 in U.S. Sales by Year from Launch

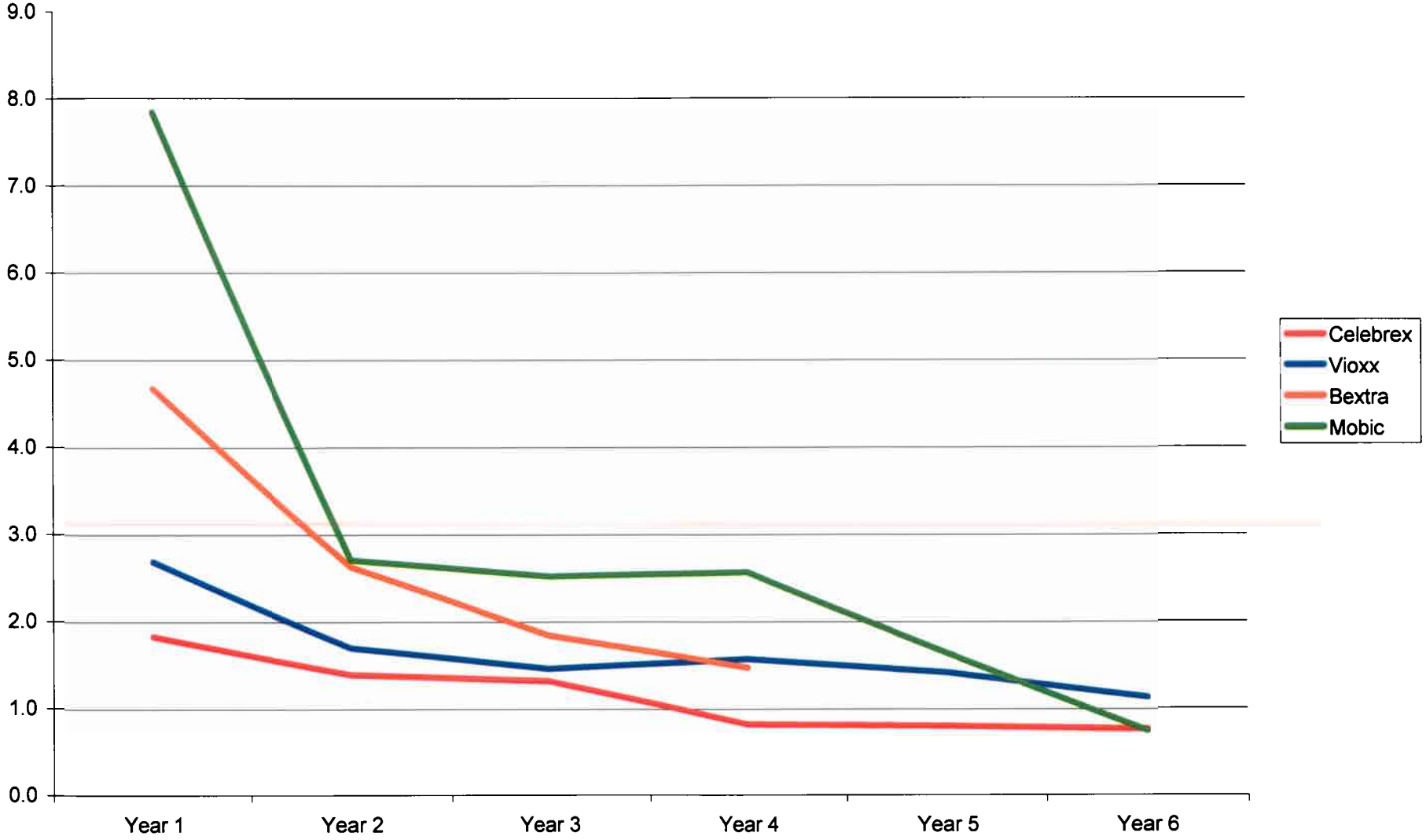


Exhibit 12

No. of Samples By Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	26,010,451	30,291,744	33,731,344	21,360,903	20,994,943	21,484,677
Vioxx	20,761,755	30,095,211	30,188,392	27,845,687	25,892,364	8,640,283
Bextra	21,180,471	24,720,271	23,163,382	2,566,254		
Mobic	5,721,735	5,332,426	6,126,124	8,831,841	12,062,964	8,114,208

* Source: 1999-2006 Verispan, PSA

U.S. Sales By Year from Launch (in $ millions)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex®	1,418	2,167	2,549	2,586	2,600	2,787
Vioxx®	772	1,770	2,061	1,770	1,824	760
Bextra®	453	940	1,255	174		
Mobic	73	197	243	344	736	1,083

* Source: 1999-2006 IMS data, "National Sales Perspectives"

Ratio of Samples/$100 U.S. Sales by Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	1.8	1.4	1.3	0.8	0.8	0.8
Vioxx	2.7	1.7	1.5	1.6	1.4	1.1
Bextra	4.7	2.6	1.8	1.5		
Mobic	7.8	2.7	2.5	2.6	1.6	0.7

Exhibit 13

Exhibit 13: Ratio of Samples/U.S. Prescriptions by Year of Launch

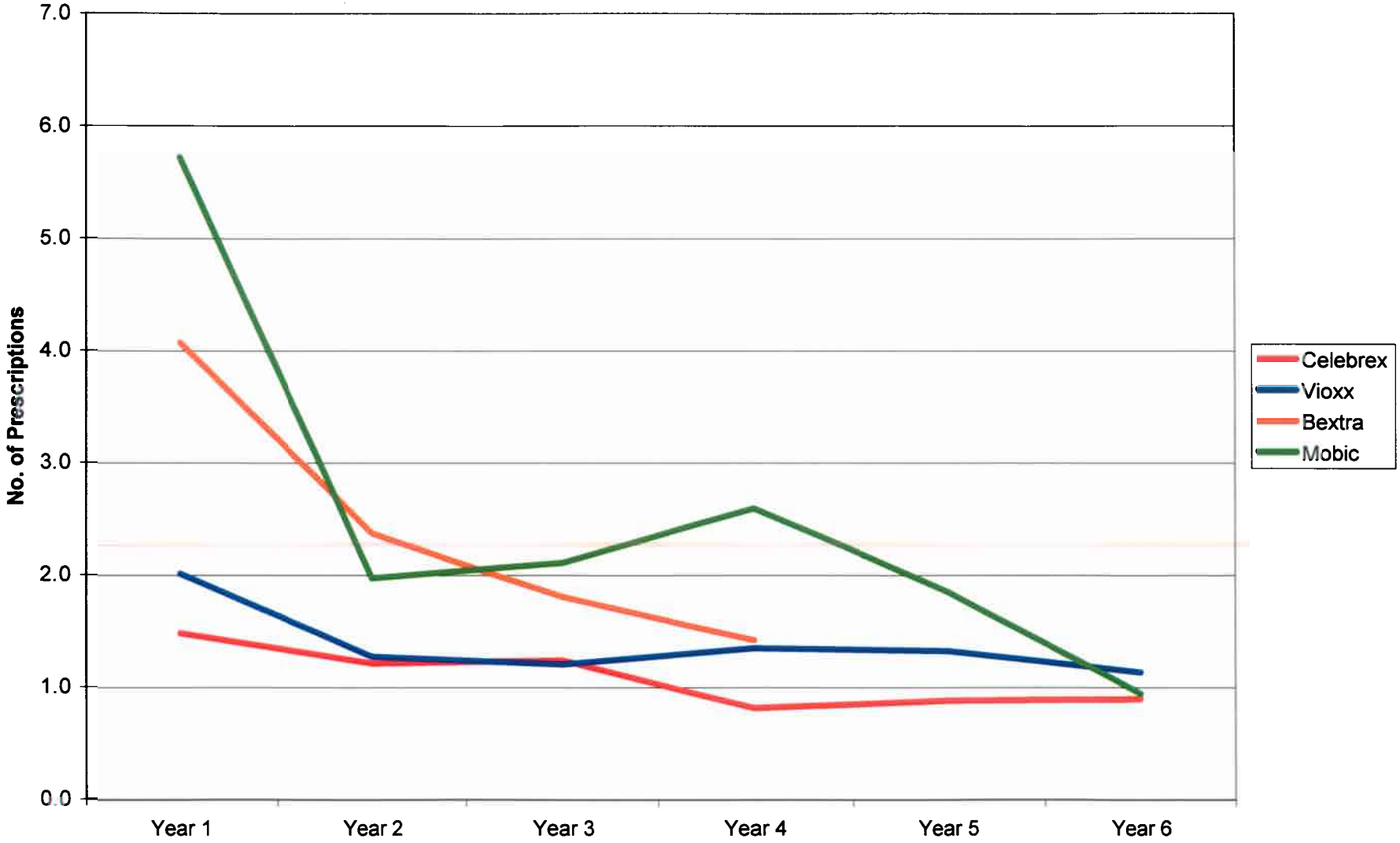


Exhibit 13

No. of Samples By Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	26,010,451	30,291,744	33,731,344	21,360,903	20,994,943	21,484,677
Vioxx	20,761,755	30,095,211	30,188,392	27,845,687	25,892,364	8,640,283
Bextra	21,180,471	24,720,271	23,163,382	2,566,254		
Mobic	5,721,735	5,332,426	6,126,124	8,831,841	12,062,964	8,114,208

* Source: 1999-2006, Verispan, PSA

Total U.S. Prescription By Year from Launch ('000)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex®	17,500	24,900	27,100	26,000	23,700	23,900
Vioxx®	10,300	23,600	25,000	20,600	19,500	7,600
Bextra®	5,200	10,400	12,800	1,800		
Mobic	1,000	2,700	2,900	3,400	6,500	8,600

* Source: 1999-2006 IMS data, "National Prescription Audit"

Ratio of Samples/U.S. Prescriptions by Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	1.5	1.2	1.2	0.8	0.9	0.9
Vioxx	2.0	1.3	1.2	1.4	1.3	1.1
Bextra	4.1	2.4	1.8	1.4		
Mobic	5.7	2.0	2.1	2.6	1.9	0.9

Exhibit 14

Exhibit 14: U.S. Promotional Spending as a % of Total U.S. Sales

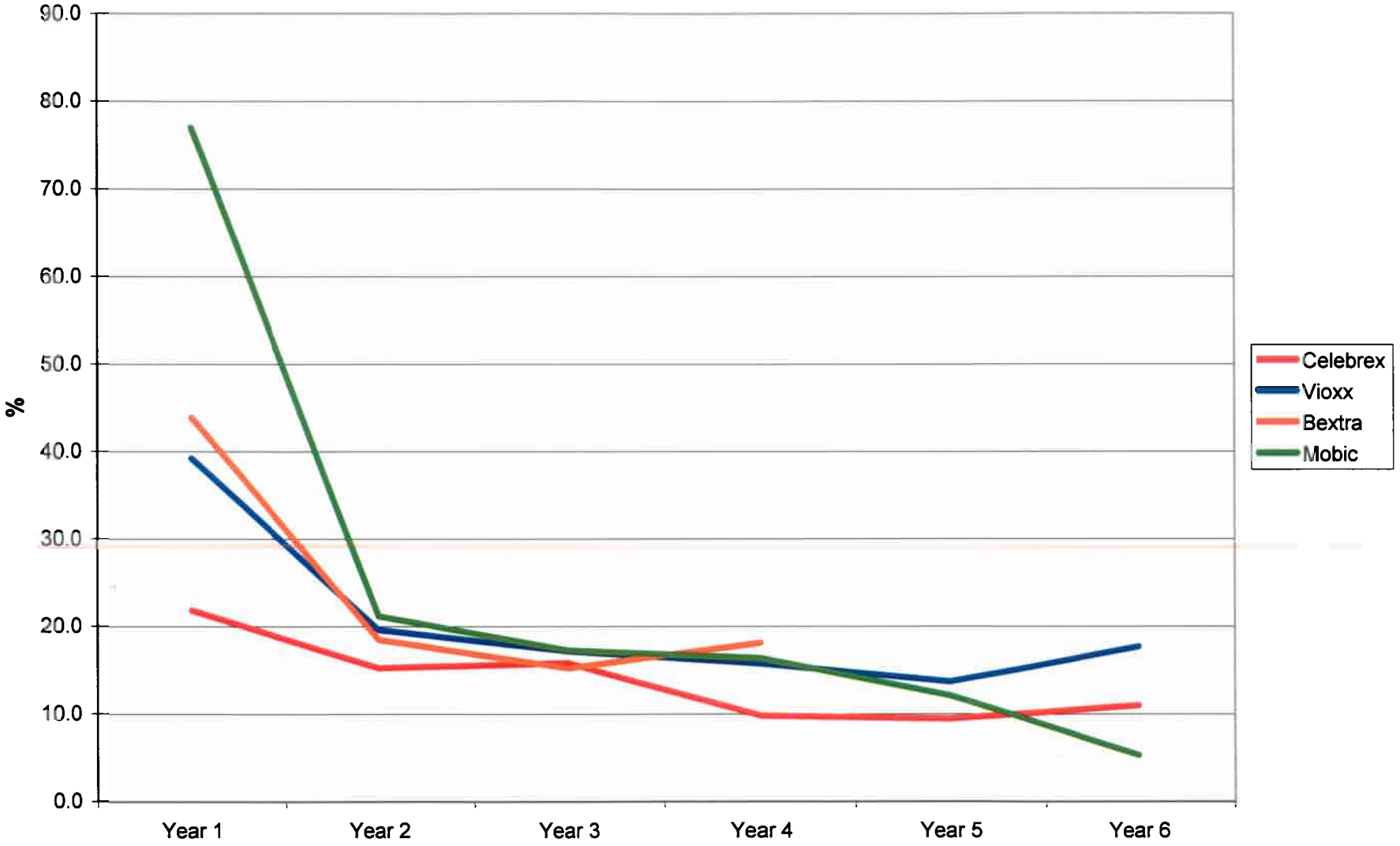


Exhibit 14

U.S. Sales By Year from Launch

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex®	1,418	2,167	2,549	2,586	2,600	2,787
Vioxx®	772	1,770	2,061	1,770	1,824	760
Bextra®	453	940	1,255	174		
Mobic	73	197	243	344	736	1,013

* Source: 1999-2006 IMS data, "National Sales Perspectives"

U.S. Promotional Spending by Year from Launch
(Detail/Professional Medical Information/Direct-to-Consumer/Journal)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	309,906,000	331,164,000	404,514,000	254,444,000	246,539,000	307,174,000
Vioxx	303,093,000	347,315,000	354,273,000	278,981,000	249,814,000	134,699,000
Bextra	198,766,000	173,836,000	191,435,000	31,592,000		
Mobic	56,218,000	41,722,000	41,988,000	56,299,000	89,170,000	53,804,908

* Source: 1999-2006 Verispan, PSA, HPSA, PMEA, DTCA/CMR, PJA

U.S. Promotional Spending as a % of Total U.S. Sales

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Celebrex	21.9	15.3	15.9	9.8	9.5	11.0
Vioxx	39.3	19.6	17.2	15.8	13.7	17.7
Bextra	43.9	18.5	15.3	18.2		
Mobic	77.0	21.2	17.3	16.4	12.1	5.3

Sales and Promotional Spending for Mobic in Year 6 is from May, 2005-March, 2006. Data for April 2006 was not availabile at the time this report was submitted. I reserve the right to include data after March, 2006 when such data becomes available.

Exhibit A

Exhibit A
Documents Reviewed

Production Documents:

PFC00222702 - PFC00222743	PFC00222744 - PFC00222774	PFC00222806 - PFC00223000
PFC00224094 - PFC00224213	PFC00228847 - PFC00228856	PFC00756191 - PFC00756193
PFC01188817 - PFC01188838	PFC01189353 - PFC01189394	PFC01190113 - PFC01190124
PFC01190934 - PFC01190938	PFC01191107 - PFC01191111	PFC01191112 - PFC01191125
PFC01191555 - PFC01191738	PFC01191739 - PFC01191743	PFC01192345 - PFC01192518
PFC01192696 - PFC01192737	PFC01193822 - PFC01193912	PFC01193956 - PFC01194066
PFC01194067 - PFC01194103	PFC01194158 - PFC01194169	PFC01194170 - PFC01194214
PFC01194215 - PFC01194412	PFC01194990 - PFC01195037	PFC01227312 - PFC01227357
PFC01236169 - PFC01236177	PFC01236926 - PFC01236939	PFC01236940 - PFC01236950
PFC01236951 - PFC01237017	PFC01237172 - PFC01237179	PFC01239508 - PFC01239540
PFC01269974 - PFC01270062	PFC01309661 - PFC01309712	PFC01534430 - PFC01534486
PFC01534487 - PFC01534541	PFC01534542 - PFC01534594	PFC01534711 - PFC01534896
PFC01534897 - PFC01534937	PFC01579032 - PFC01579067	PFC01579924 - PFC01579942
PFC01580538 - PFC01580553	PFC01584998 - PFC01585001	PFC01593451 - PFC01593453
PFC01593532 - PFC01593567	PFC01593878 - PFC01593927	PFC01593928 - PFC01593964
PFC01594029 - PFC01594099	PFC01594100 - PFC01594181	PFC01594274 - PFC01594426
PFC01594427 - PFC01594571	PFC01594572 - PFC01594748	PFC01594749 - PFC01594956
PFC01597032 - PFC01597358	PFC01597359 - PFC01597456	PFC01598212 - PFC01598248
PFC01598275 - PFC01598275	PFC01598304 - PFC01598305	PFC01602622 - PFC01602626
PFC01602627 - PFC01602662	PFC01602674 - PFC01602676	PFC01602677 - PFC01602679
PFC01603194 - PFC01603199	PFC01603268 - PFC01603276	PFC01603507 - PFC01603510
PFC01604139 - PFC01604174	PFC01604283 - PFC01604298	PFC01604397 - PFC01604437
PFC01605650 - PFC01605695	PFC01606410 - PFC01606411	PFC01606412 - PFC01606413
PFC01606490 - PFC01606491	PFC01606504 - PFC01606506	PFC01606507 - PFC01606509
PFC01606654 - PFC01606656	PFC01606657 - PFC01606660	PFC01606661 - PFC01606662
PFC01607006 - PFC01607041	PFC01607081 - PFC01607092	PFC01607097 - PFC01607116
PFC01607124 - PFC01607155	PFC01607251 - PFC01607271	PFC01607307 - PFC01607327
PFC01607328 - PFC01607342	PFC01607343 - PFC01607381	PFC01607382 - PFC01607383
PFC01607627 - PFC01607648		

Deposition Exhibits:

DX 342	DX 342
DX 343	DX 345
DX 346	DX 347
DX 349	

Expert Reports:

Galbraith	5/5/2006

Helfgott	5/5/2006
Iannini	6/23/2006
Leffler (and exhibits)	5/5/2006
Schultz	5/5/2006
Seibert	6/23/2006
Wolfe	5/5/2006

Other:

1999 Verispan DTC data (showing no Celebrex spending in July-August 1999);
DiMasi and Paquette, “The Economics of Follow-on Drug Research and Development,” Pharmacoeconomics, Vol. 22 Suppl. 2, 1-14 (2004).
Grabowski And Mullins, "Pharmacy Benefit Management, Cost Effectiveness Analysis, And Drug Formulary Decisions," Social Science And Medicine, 45 (1997) 535-44 (1997). ;
Iizuka, "What Explains the Use of Direct-to-Consumer Advertising of Prescription Drugs?," J. of Indus. Eco., Vol. LII, No. 3, pp.349-379 (2004).
Juni et al, "Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs?" BMJ. 324: 1287-1288 (2002).
Mallaby, "A Worm at the Core of Capitalism," Washington Post, Monday, p. A21(2002).
PhRMA 2000 Pharmaceutical Industry Profile;
Schnaars, “Managing Imitation Strategies: How Later Entrants Seize Markets From Pioneers,” The Free Press (1994)